EXHIBIT B

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UNITED STATES BANKRUPTCY COURT
SOUTHERN DISTRICT OF NEW YORK

In re:	:	Chapter 11
PURDUE PHARMA L.P., *et al*.,	:	Case No. 19-23649 (RDD)
Debtors[1]	:	(Jointly Administered)

REPLY OF THE NAS CHILDREN AD HOC AND SUPPLEMENTAL DECLARATION IN FURTHER SUPPORT OF ITS REQUEST FOR ENTRY OF A COURT ORDER AUTHORIZING EXAMINATIONS PURSUANT TO FEDERAL RULES OF BANKRUPTCY PROCEDURE 2004 AND 9006

The NAS Children Ad Hoc Committee ("**NAS Children Ad Hoc**"), through its counsel, Tarter Krinsky & Drogin LLP, respectfully submit this Reply in response to Debtors' Objections ("**Objections**") [Dkt. No. 2155] to NAS Ad Hoc Committee's Motion for Entry of an Order Pursuant to 11 U.S.C. §§ 105(a) and 107(b) and Fed. R. Bankr. P. 9018 Authorizing a Filing of

[1] The Debtors in these cases, along with the last four digits of each Debtor's registration number in the applicable jurisdiction, are as follows: Purdue Pharma L.P. (7484), Purdue Pharma Inc. (7486), Purdue Transdermal Technologies L.P. (1868), Purdue Pharma Manufacturing L.P. (3821), Purdue Pharmaceuticals L.P. (0034), Imbrium Therapeutics L.P. (8810), Adlon Therapeutics L.P. (6745), Greenfield BioVentures L.P. (6150), Seven Seas Hill Corp. (4591), Ophir Green Corp. (4594), Purdue Pharma of Puerto Rico (3925), Avrio Health L.P. (4140), Purdue Pharmaceutical Products L.P. (3902), Purdue Neuroscience Company (4712), Nayatt Cove Lifescience Inc. (7805), Button Land L.P. (7502), Rhodes Associates L.P. (N/A), Paul Land Inc. (7425), Quidnick Land L.P. (7584), Rhodes Pharmaceuticals L.P. (6166), Rhodes Technologies (7143), UDF L.P. (0495), SVC Pharma L.P. (5717) and SVC Pharma Inc. (4014).

Certain Information and Exhibits Under Seal in Connection with the NAS Children Ad Hoc Committee's Ex Parte Motion Requesting a Court Order Authorizing Examination Pursuant to Fed. R. of Bankr. P. 2004 and 9006. (the "**Rules**") (the "**Motion**") [Dkt. No. 2139], together with the accompanying Supporting Declaration of Donald Creadore, Esq. dated March 10, 2021 in further support of the relief requested in the Motion is annexed hereto as **Exhibit A** (the "**Supp. Dec**.")**.**

PRELIMINARY STATEMENT

1. It is axiomatic that the determination of causation abounds in matters relating to personal injuries. Not until the [redacted]

2. The NAS Children simply do not have time to continue to engage in a scavenger hunt in the tens of millions of pages that the Debtors have produced using the search term method. Rather, pre-ESI discovery where narrow categories of documents are requested, producing parties' personnel locate responsive documents and lawyers turn them over is the only way that the NAS Children can successfully navigate the vague and overburdened position created by the Debtor's Disclosure Statement.

3. Contrasting the Debtors' responsiveness to the [redacted] illustrates this point. Although several copies of [redacted] document appear in massive document production provided by the Debtors, it only came to the NAS Children's attention when it was easily found [redacted] In that document, "[redacted]", the [redacted] agree "t[redacted]

[redacted]. See Attached **Exhibit A to Supp. Dec**., [redacted]", IACS_ESI_0001409172.

4. Specifically, the following statements, from documents produced by Debtors to the NAS Children Ad Hoc, are a representative sampling of a larger body of information underscoring Debtors' knowledge of causal risks of fetal exposure to its opioids and, separately, the delay in reacting to it, exacerbating a public health crisis:

[redacted]

See **Exhibit A to Supp. Dec**. at IACS_0001409181

[redacted]

See **Exhibit A to Supp. Dec**. at IACS_0001409182

[redacted]

See **Exhibit A to Supp. Dec.** at IACS_0001409185.

5. The NAS Children Ad Hoc has been diligently seeking production of evidence relating, referring or concerning issues surrounding Debtors' liability and medical causation of

their injuries. Accordingly, it is both warranted and justified that the Debtors be ordered to immediately produce, in entirety, all toxicology studies (e.g., pre-clinical; good laboratory practices (GLP) and non-GLP, alike; lab notes; and internal white papers) concerning pure, synthetic, and semi-synthetic opioids, along with a detailed index of such materials, whether produced to the FDA or not, within Debtors' possession, custody or control. Additionally, Debtors should be ordered to produce for oral examination under oath certain custodians of records and other individuals to be identified and agreed upon. All of the foregoing discovery can be contained in a proper scheduling order.

I. DEBTORS' RESPONSES ARE INADEQUATE AND OVERDUE

a. Debtors' Maintain A Knowledge Bank of Scientific Information.

6. By way of background, according to its website, "Purdue and its subsidiaries is a pioneer in medical science with a patient-first approach in developing prescription and non-prescription medications."[2] Suffice to say, pharmaceutical leaders generate an extraordinary amount of medical and scientific literature, research, analysis, results, data, content, and similar materials.[3]

b. Full Production and Testimony Regarding Debtors' Embryo –Fetal Animal Testing is Warranted.

7. As a byproduct of the research and development of its pharmaceutical products, the Debtors have established and compiled a significant—perhaps the leading—body of scientific and

[2] *https://www.**purduepharma**.com/healthcare-professionals/products*, accessed February 20, 2021.

[3] Competitors like, for example, Bristol-Myers Squibb are being presented by medical content consultants as case studies that promote the virtues and benefits for a centralized repository, including: (I) Medical content is controlled by the source content owners. (II) Complete control over versions in use. (III) Avoidance of duplication. (IV) Ability to connect Parent/Child information along world-wide, regional, local platforms. (V) Centralized source of all regulatory materials; ease of reference, distribution, and updating and archiving. (VI) Centralized source of all research and development tests and studies; ease of reference and archiving. (VII) Centralized control over labeling and warnings requirements internationally, regionally, or locally. (VIII) Centralize product registration data worldwide, including registration status, variations, and health authority interaction.

medical knowledge regarding embryo-fetal opioid exposure and, similarly, risks associated with maternal use of opioids. Debtors' medical and science "knowledge bank" is known to contain valuable one-of-a-kind medical assets of great interest to the NAS Children Ad Hoc, such as the body of information and research data associated with and generated through a full complement of embryo-fetal reproductive studies Debtors had commissioned concerning, for example, rats and New Zealand White rabbits; see, e.g., paragraphs 23-24, *infra*. The recent revelation of the existence of an array of rat and rabbit studies evaluating embryo-fetal results, adverse effects, side effects, and risks, *and* studies relating to in vitro chromosomal aberrations, *of oxycodone hydrochloride,* is sufficient cause for the NAS Children Ad Hoc to request full and unrestricted disclosure of this information in connection with efforts to establish the extent of injuries sustained and, as a consequence, Debtors' liability to NAS Claimants**.**

8. The series of citations to embryo-fetal animal studies referenced among documents produced by Debtors strongly suggests that other, similar, studies may also have been conducted but not submitted to the FDA as part of Debtors' new drug application ("**NDA**") or Abbreviated New Drug Application ("**ANDA**") for oxycodone hydrochloride. The Debtors also leave open the possibility of other relevant information existing but not produced when declaring, "the NAS Committee already has all of the information *that was required to be (and was) made available to the FDA* as part of each product NDA." See Objection at ¶ 8 (underline in original, italics added). Debtors' 1994 Archival New Drug Application ("**ANDA**") contains an explicit reference to

conducting non-GLP studies, albeit in this example upon non-pregnant animals[4], i

See , annexed as **Exhibit B to Supp. Dec**.

Debtors' ANDA goes on to summarize various conclusions derived from Debtors' non-GLP range finding studies. However, the underlying testing data, protocols and processes, and conclusions. surrounding Debtors' performance of non-GLP studies and range-finding (and range-dosing) studies, has not been disclosed through testimony under oath; limiting Debtors' discovery duties to only document production and excluding testimony under oath presents unwarranted, unexpected, and undue hardship to the NAS Claimants. There is no valid reason excusing Debtors' obligations to produce witnesses to substantiate the information contained in the documents Debtors produced in this case to the NAS Children Ad Hoc. Oddly and without any witness substantiation Debtors continue to informally deny, through their lawyers, the existence of additional studies not produced to the FDA describing, concerning, referring or relating to risks and adverse events and side effects—many life-altering and lifelong—due to fetal exposure to their

[4]

opioid drugs, such as oxycodone hydrochloride. As a result, NAS Claimants stand to endure undue hardship due absent full disclosure by Debtors, through document disclosure and testimony.

c. <u>Production and Testimony Regarding Debtors' Company Core Data Sheet is Warranted.</u>

9. From what can be adduced from the body of information produced so far by the Debtors there exists a corporate research and development compendium of knowledge about Oxycodone Hydrochloride, more commonly referred by Debtors as t[redacted], Oxycodone Hydrochloride (the "[redacted])[5]. Like the United States Constitution, *the titles* to each of the 10 sections[6] that comprise Debtors' [redacted] remain unchanged throughout the process of updating it with a superseding version (of Debtors' [redacted]). However, by distinction, the titles of subsections and entries to subsections to Debtors' [redacted] have been amended by Debtors over the two decades, or more, of its documented existence.

10. The process of amending a subsection to Debtors' [redacted] appears to be duly recorded and meticulously documented and, seemingly, the subject of intense debate among Debtors' research and medical communities and consultants (prior to the proposed language amending any subsection is incorporated into any approved superseding version of the [redacted]); a process that—in the instance of amending the [redacted], Version 11.0, to [redacted]

[5] Upon information and belief, Debtors maintain similar but separate [redacted] for Morphine, Hydromorphone and other drugs.

[6] The topic headings are as follows: [redacted] 2. [redacted] 3. [redacted] 4. [redacted] 5. [redacted] 6. [redacted] 7. [redacted]; 8. [redacted]

[redacted].[7]

11. [redacted] is regularly updated. Since 2000, there appears to be no less than [redacted], according to the information adduced from the documents produced to the NAS Children Ad Hoc.[8] The NAS Children Ad Hoc has adequate reason and justification to request disclosure of all of the versions of the [redacted], from [redacted] each of which is explicitly (and conveniently) referenced in **Exhibit C-3 to Supp. Dec.**, [redacted] Debtors should also be ordered to produce one or more records' custodians with requisite knowledge and authority of the [redacted]; for example, the persons whose name appears on the face page or signature page of one or more [redacted]

d. The Evolution of Entries in the [redacted] for Fertility, Pregnancy and Lactation.

12. The evolution of Debtors' entries to the [redacted] section to its [redacted] is disturbing to the NAS Children Ad Hoc.

In 2002, the [redacted] contained the following one entry to [redacted], to wit:

> [redacted]

[redacted] as **Exhibit C-1 to Supp. Dec**. (footnotes original)

[7] According to the information provided by Debtors the following additions were officially approved and incorporated into the [redacted]

[8] See, [redacted] Vol 13.0, pp. 2-6 of 26 [April 5, 2017]

In 2003, an additional (second) entry was added as an amendment to the [redacted] to wit:

[redacted]

See, [redacted] as **Exhibit C-2 to Supp. Dec.)** (footnotes original)

In 2017, an additional (third) entry was added as an amendment to [redacted] to wit:

[redacted]

See, [redacted] as **Exhibit C-3 to Supp. Dec.** (footnotes in original)

13. [redacted] by "M. Sturm"—then Senior Medical Manager for European Drug Safety & Pharmacovigilance and QPPV for Mundipharma Germany—t[redacted] "**Sturm** [redacted]"). The Sturm [redacted] is, more likely than not, both material and relevant to NAS Children Ad Hoc, and to the NAS Abatement Program (or, similarly, may lead to relevant and material information), but it appears that Debtors have yet to produce it without explanation nor justification. It is incumbent upon Debtors to justify through testimony under oath the soundness of reasoning, dialogue, and timing, behind all of the amendments of concern to individuals, and in

[9] The origins of the addition of [redacted] to this subsection is currently unknown by the NAS Children Ad Hoc. Notwithstanding, the NAS Children Ad Hoc contends that the addition is noteworthy and just not an afterthought on the Debtors' part.

the case of NAS Claimants why Debtors did not seek to amend its [redacted] to incorporate neonatal opioid withdrawal syndrome ("**NOWS**") prior to 2013, especially where, like here, the Debtors seemingly had notice, knowledge and possession of the Sturm [redacted] flagging this risk or related risks as far back as 2002.

14. It appears to the NAS Children Ad Hoc that Debtors had also learned about the risks and adverse effects and possible side effects of their opioid products to fetal development from their international affiliates associated with Mundipharma, as early as 2011, three years before the risks of "neonatal opioid withdrawal syndrome" was added to Debtors' [redacted] Version 11.0. Indeed, in a May 5, 2011 e-mail string, titled "[redacted]", Michael Sturm [redacted] Catherine Evans, Senior Medical Information Scientist at Purdue, responds by attaching a full scan of the article[10] [redacted] (1) buprenorphine, (2) oxycodone, (3) hydromorphone, and (4) morphine, as described in the medical reference guide titled Drugs in Pregnancy and Lactation, 8th Edition. *See* May 5, 2011 Emails, IACS_ESI_003502069, annexed as **Exhibit H to Supp. Dec**.[11] These four entries contained in the Pregnancy & Lactation Reference Guide are, in large part,

[10] In actuality, the 'article' being referenced appears to consist of excerpts relevant to these four (4) drugs from the medical reference guide titled Drugs in Pregnancy and Lactation, 8th Edition (the 9th Edition is now publicly available from, for instance, Amazon) (the "**Pregnancy & Lactation Reference Guide"**).

[11]Debtors have provided pertinent portions of the reference guide Drugs in Pregnancy and Lactation, 8th Edition, pertaining to buprenorphine, morphine, hydromorphone and oxycodone but, regrettably, on only a view-only platform, preventing any reproduction and needlessly complicating the process of review, adding delay. On its own accord, the NAS Children Ad Hoc duly reviewed the 9th Edition of this same published medical reference guide on a public platform and have reproduced only the relevant excerpts as an exhibit.

presented in the form of a "breast feeding summary" and a "fetal risks summary"; and certain excerpts reproduced from the 9th Edition are annexed as **Exhibit E to Supp. Dec.** [12]

15. The following fetal risks summaries describe adverse events and risks of fetal opioid exposure:

> **Hydromorphone**
> Fetal Risk Recommendation: **Human Data suggests Risk in 3rd Trimester.**
> Hydromorphone is **excreted into breast milk.**

See Id., at IACS_ESI_0003502077, Drugs in Pregnancy and Lactation, 8th Ed., reprinted here from 9th Ed.

> **Oxycodone**
> Fetal Risk Recommendation: **Human Data suggests Risk in 3rd Trimester.**

See Id., at IACS_ESI_0003502075, Drugs in Pregnancy and Lactation, 8th Ed., reprinted here from 9th Ed.

> **Morphine**
> Pregnancy Recommendation: **Human Data suggests Risk in 3rd Trimester.**

See Id., at IACS_ESI_0003502072, Drugs in Pregnancy and Lactation, 8th Ed., reprinted here from 9th Ed.

16. Both reason and logic inexorably lead to a presumption that, as a self-proclaimed pioneer and leader of opioids production and marketing, Debtors both performed and commissioned their own comprehensive studies evaluating the scope of the risks, and side effects and adverse events, arising from, caused by, or related or due to exposing embryos and fetuses to its opioids. Against the weight of the documentary proof produced by them in this case, Debtors repeatedly tell the NAS Children Ad Hoc that Debtors are unaware of any other pre-clinical studies on these subjects. It has been left to the NAS Children Ad Hoc to uncover information that is

[12] NAS Children Ad Hoc duly reviewed the 9th Edition of this same published medical reference guide on a public platform and have reproduced only the relevant excerpts as an exhibit.

useful in understanding issues of causation of fetal opioid exposure and, as a consequence, the extent of Debtors' liability to NAS Claimants, causing undue hardship.

17. Depriving NAS Claimants from discovery of *the entirety of all* material and information, including Debtors' Scientific Information[13], both relevant and beneficial to them is not only counterproductive it is also unfair and unwarranted and would serve to deny them due process. On a grander scale, an examination and evaluation of Debtors' probity, integrity and honesty regarding issues surrounding causation and Debtors' liability can assist this Court whenever exercising its equitable powers to discharge Debtors' liability or, similarly, awarding broad releases to certain non-parties; and, here, the information and material being sought also relates to Debtors' probity, integrity and honesty. Accordingly, immediate release of the information will be beneficial to the Court in addition to the NAS Children Ad Hoc and, more likely than not, other parties.[14]

18. By virtue of the existence of an array of scientific and medical information and content contained within the documents produced thus far by Debtors, including citations to genotoxicity, mutagenicity, chromosomal aberrations, GLP and non-GLP range-dosing and pre-clinical and embryo-fetal animal studies, it stands to reason that other medical information and content, and relevant studies remain within Debtors' possession, custody, or control. Without justification, Debtors are withholding a body of relevant and material information and, seemingly, unwilling to release any of it without a court order, causing undue hardship.

[13] Scientific Information for this motion includes the further production of medical and scientific information, research, data, studies, and materials currently within the possession, custody, or control of Debtors.

[14] It stands to reason that adult women of child-bearing age will also directly benefit from revelations regarding risks of maternal use of opioids to be derived from disclosure of the information requested.

19. In sum, it is undeniable that Debtors have produced documents containing entries explicitly referencing pre-clinical studies being conducted on their opioid drugs, but it also stands to reason that not all of the underlying studies and research has been disclosed to the NAS Children Ad Hoc. Also undeniable is the fact that Debtors are also withholding information relevant and material to Debtors' determination, in and about 2014, to update the [redacted] by amending a subsection pertaining to fertility, pregnancy and lactation to include the following explicit reference: "[redacted]". See, [redacted] Upon information and belief, some or all of this information may have been withheld from various state, federal and foreign regulators.

e. [redacted]

20. The NAS Children Ad Hoc has uncovered entries on documents produced by Debtors, [redacted] explicitly referencing '[redacted]; the number of entries is too great to ignore.

21. So far, the NAS Children Ad Hoc has information suggesting Debtors' [redacted] consists of no less than 105 volumes, according to a full reference citation (e.g., by volume and subsection, and volume date) to '[redacted] When the NAS Children Ad Hoc [redacted] they advised that it was owned and operated by Debtors. Swimming against a tidal wave of [redacted] is Debtors' flat declaration that "[redacted]"; this stance has hindered all further cooperation on this topic. A true and correct copy of Debtors' communication is annexed as **Exhibit F to Supp. Dec.**

22. Additional confirmation seemingly substantiating the existence of a [redacted] is found, tellingly, among Debtors' electronic communications that

contain references to (i) oxycodone and/or to (ii) the [redacted] ***that also*** explicitly cites (by volume, section and by date range) presumed contents of a "[redacted]" For instance, in an email thread from [redacted] regarding an ongoing debate over recommended edits to the then-prevailing [redacted] (upon information and belief, either version [redacted]), then-Purdue advisor, Nienke Smilde, tells Purdue's Vice President for Medical Affairs and Worldwide Drug Safety, Robert F Reder, MD, that he (Smilde) is, "[redacted]". A true and correct copy of the [redacted] Email Thread, PPLP0028000094094, is annexed as **Exhibit G to the Supp. Dec.**

23. Suffice to say, the numerous internal references and communications surrounding a "[redacted]" appearing on documents produced by Debtors, coupled with the r[redacted] rightfully begs the question of whether this '[redacted]' is, as Debtors profess, a fiction or rather, [redacted] a reality. It appears that this question can be resolved only by a court order demanding that Debtors not only provide a comprehensive and factually-supported explanation but also produce an exhaustive listing of any document '[redacted]' of scientific information currently in existence or formally existing, supplemented by testimony under oath.

24. In sum, the sheer volume of documentary evidence produced by the Debtors establishing the existence of a wealth of information relating, referring or concerning the [redacted] directly in the face of Debtors' terse and unequivocal representations that "[redacted]" The NAS Children Ad Hoc has no reason to doubt the accuracy of the statements from non-parties possessing requisite knowledge and, here, the IACs satisfy these qualifications. While the NAS Children Ad Hoc is cognizant that Debtors' [redacted] may consist of one or more

(a) three-ring binder(s), (b) floppy diskettes or similar, (c) banker's boxes or file drawers, (d) an office facility, or just a full unedited version of the NDA, it is incumbent upon Debtors to fully and comprehensively address and disclose all matters regarding the [redacted] and to produce the appropriate records custodian(s) for examination, in addition to other individuals possessing requisite knowledge. Accordingly, without Court intervention at this juncture, there is no legitimate or lawful means, nor jurisdiction, to guarantee that the assets of greatest interest to the NAS Children Ad Hoc—indeed, to ALL individuals that have been exposed, voluntarily or involuntarily, to Debtors' opioids products—currently in Debtors' knowledge bank will be made available at the time when most needed by them--now.

25. It bears repeating that immediate and full disclosure of the Scientific Information and related information is (1) critical to NAS Claimants and, separately, to the professionals and staff laying the groundwork for a timely and successful launch and implementation of the NAS Abatement Program to provide immediate relief to the countless families caring for a child suffering from fetal opioid exposure; and (2) will provide women of child-bearing age with additional information addressing all of the potential health risks, side effects and adverse events—many life-altering and lifelong—upon human embryos and fetuses due to *in utero* opioid exposure through maternal use of opioids. Debtors' immediate disclosure of the requested information, together with disclosure of other materials presently sought and to be sought, will serve to advance all-important goals of mitigating the opioid epidemic and improving lives.

f. Debtors' Research and Development 'Constitution', or [redacted]

26. From what can be adduced from the body of information produced so far by the Debtors, there exists a corporate research and development compendium of knowledge, commonly known to the Debtors as the [redacted] it appears that Debtors

maintain a unique [redacted] for a large number, if not all, of its pure, synthetic, and semi-synthetic opioids. Like the United States Constitution, [redacted] have remained unchanged throughout the process of updating it with superseding versions [redacted] However, [redacted] belonging to each of the [redacted] are amended. The process of [redacted] appears to be duly recorded and meticulously documented and, seemingly, the subject of intense debate among Debtors' research and medical communities and consultants before any language amending a subsection is incorporated into any approved superseding version of the [redacted] a process that—in the instance of [redacted] can span many years.[15] The Debtors regularly update the [redacted] since 2000, there appears to be no less than [redacted] according to the information adduced from the documents produced to the NAS Children Ad Hoc.[16] The NAS Children Ad Hoc has adequate reason and justification to request disclosure of all of the versions of the [redacted] including but not limited to version 1 through and including version 13, each of which is explicitly (and conveniently) referenced in **Exhibit C-3 to the Supp. Dec**, [redacted] PPLPC056000665626.

II. Debtors' Objections Are Unpersuasive and Unavailing:

a. Debtors' Mischaracterization and Dismissal of Animal Studies Lacks Merit.

27. The Debtors' knowledge bank of assets includes animal studies both material and of current value, benefitting of creditors. It is undisputed that the Debtors have engaged in pre-clinical animal testing and, further, Debtors acknowledge maintaining [redacted]

[15] See footnote 7.

[16] See, **Exhibit C-3 to Supp. Dec.**, [redacted]

[redacted] in addition to disclosing the following set of "[r]eproductive studies related to oxycodone use in animal models:"

- DSE–058 - Reproductive (embryo-fetal—Segment II) Range-Finding Study– Rabbit
- DSE–059 - Reproductive (embryo-fetal—Segment II) Range-Finding Study–Rabbit
- DSE–060 - Reproductive (embryo-fetal—Segment II) Range-Finding Study–Rat:
- DSE- 061- Reproductive (embryo-fetal—Segment II) – Rat In Vitro Chemical Chromosomal aberration.

See **Objection** at ¶. 7.

28. This short list of studies furnished by Debtors leaves open for suggestion that studies had been conducted but not submitted to the FDA as part of the licensing and approval of Purdue's opioid medications. Indeed, Debtors concede to curating its production by openly declaring "the NAS Committee already has all of the information *that was required to be (and was) made available to the FDA* as part of each product NDA." See **Objection** at ¶ 8 (underline in original, italics added).

29. Debtors assert their "belief" that the current studies being sought by the NAS Children Ad Hoc "relate to a hydromorphone product never at the heart of the underlying litigation…" Objection at ¶ 1. This gratuitous statement is simply inaccurate and mischaracterizes the facts and circumstances. The NAS Children Ad Hoc is uncertain of the basis of Debtors' expressed "belief" without further explanation. Suffice to say, the NAS Children Ad Hoc has an unremitting interest in animal studies relating to pure, synthetic and semi-synthetic drugs, including oxycodone and, tellingly, Debtors cite to a series of embryo-fetal reproductive studies concerning oxycodone, exclusively. See, Objections at ¶ 7. Curiously, Debtors have never

attempted to explain why the disclosure of similar reproductive studies concerning other pure, synthetic, and semi-synthetic drugs, would not benefit the NAS Children Ad Hoc. It is widely known that, as a matter of an oral dosage conversion, a hydromorphone product is four times more powerful than an oxycodone product.[17]

30. Given the Debtors' qualified statement that the production to date is limited to "the FDA [imposed requirements] as part of each product NDA;" it stands to reason that additional information is both ascertainable and available for production.

31. Debtors contend, without authority, that animal toxicology is only "hypothesis generating", Objections at ¶13; this proposition is needlessly disingenuous and woefully incomplete. No less authority than the Society of Toxicology, on its website, observes that "Animal studies help determine the ratio between the beneficial dose and the toxic dose of medications." Toxicologists determine which levels of a substance cause harm by conducting safety studies which progress from the test tube to animal studies and, in some cases, to human trials. Safety testing is needed to identify the crossover points between no impact, beneficial effects and harmful effects."[18] The NAS Children Ad Hoc respectfully contends that rather than becoming mired in analysis of animal studies, Debtors should first convincingly demonstrate how their opioid drugs do not cross the placenta.

b. <u>The Requests Are Claims Related and Serve to Benefit Claimants.</u>

32. The discovery sought is consistent with a long-running effort to assist a party in interest in (1) demonstrating causation to the extent required, and (2) determining the nature and

[17] Approved Opiate Equivalent Dosing (oral): hydromorphone, 1 mg; oxycodone, 4mg; morphine, 8mg; codeine, 24 mg.

[18] "Animals in Research: The Importance of Animals in the Science of Toxicology". Brochure, National Society of Toxicology, Accessed 3/9/2021. https://www.toxicology.org/pubs/docs/air/AIR_Final.pdf. *See* Objection ¶13-14.

extent of one of Debtors' varied assets—here, Debtors' knowledge bank and its contents of Scientific Information related to fetal opioid exposure—an asset that, oddly, remains unaccounted for and, consequently, its value, currency, and noteworthiness, remain locked.[19] Unlocking this information will provide valuable assistance to NAS Claimants and, similarly, to medical professionals responsible for implementing the NAS Abatement Program. Each of these goals stands alone as a proper objective; accordingly, timely disclosure is appropriate to ensure a full recovery of Debtors' assets for the benefit of creditors. Benefits would also accrue to the medical and science communities as well as both, directly and indirectly, the multitudes of women of child-bearing age nationwide that may have been, or will be, prescribed an opioid.[20]

III. By Seeking Equity Debtors and Non-Parties Alike Must Do Equity.

a. <u>Disclosure by Debtors Comports with Precedent.</u>

33. All of the foregoing is consistent with the goals expressed in Debtors' court filings and in-court declarations, including the recently filed Plan and Disclosure Statement [respectively, Dkt. Nos. 2487 and 2488]—as well as within the spirit if not actual language relating to the contemplated issuance of broad releases to non-parties—concerning the posting of data in a usable form on a publicly available website accessible to researchers, journalists, lawyers, patients' advocates groups, and policymakers, to further understanding of the causes of the opioid epidemic

[19] Debtors' calculated and continued refusal to meaningfully address and open its knowledge bank of scientific information and research regarding exposing fetuses to opioids and, similarly, the causes of neonatal opioid withdrawal syndrome identified in Debtors' self-created [redacted], is another disturbing irony, indeed hypocrisy, when one also factors in the decades-long existence of the Sackler-Lefcourt Center For Child Development in midtown Manhattan. For reasons that should be obvious to all, the Debtors' association, if any, with the activities, finances or studies of the Sackler-Lefcourt Center For Child Development is of further interest to the NAS Children Ad Hoc.

[20] For avoidance of any doubt, as well as for purposes of completeness and fair notice, the NAS Children Ad Hoc contemplates agreeing with Debtors upon a revised, more targeted, set of Requests for Production from the group that remains unresolved subject to meet and confers. The Revised Requests for Production are requesting a targeted set of documents maintained in the normal course of business to be provided pursuant to an informal or formal scheduling stipulation. See attached **<u>Exhibit D to Creadore Declaration</u>**, Revised Requests for Production. Notwithstanding, for avoidance of doubt, the NAS Children Ad Hoc intends to seek additional discovery, and nothing herein should be construed as a waiver to additional discovery upon parties and non-parties alike.

and to implement solutions to address the opioid epidemic public health crisis. No less was expected of Debtors in a related bankruptcy, Insys Therapeutics, Inc., and there is ample precedent to apply at least the same expectations here, too. "Such disclosure [in Insys] on what has been done in the past in connection with resolution of tobacco litigation, and similar disclosure provisions have been agreed to in a recent settlement with McKinsey & Company, Inc." See, *In Re Insys Therapeutics, Inc.*, et al., 19-cv-11292-JTD (U.S. Bky. Ct., Del.), ECF-Doc 1495, at p. 5.

b. Examinations of Persons Closely Connected with Debtors Is Proper

34. It is beyond cavil that the members of the Sackler Families identified in the Motion are "persons closely connected with the bankrupt in business dealings, or otherwise," and examination is merited. Avoidance or excusal of such examination is, under the prevailing facts and circumstances, unwarranted and too great a risk to ignore; erring on the side of caution should prevail.

35. No less important is the ability of the court to independently form a sound and definite determination that the various members of the Sackler Families requesting that they be released from liability by the Court have at all times relevant dealt fairly and honestly, and with probity, prior in time to approving general releases to some, if not all of them.

36. In sum, no discharge should be considered until and unless both the Debtors *and* those members of the Sackler Families desiring a court order releasing them from liability all satisfy their burden of demonstrating that all of them, without exception, have acted honestly and with integrity and utmost probity in all respects. See, *In Re Drexel Burnham, 123 B.R* at 708.

37. As referred to in our original motion, Drs. Landau and Sackler each gave almost identical, seemingly evasive, testimony when each was directly asked whether the Debtors had

conducted toxicology studies that were not disclosed to the FDA. *See* Motion, paras. 35-37 [Dkt. No. 2139].

38. Desires by parties and non-parties to obtain a discharge, or release, cannot override the concerns of all involved that haste makes waste and can lead to an improvident resolution. "Reasonable examination should not be allowed to be checked by constant objections that the materiality of the answer may not be immediately apparent, where no harm can arise to the witness from the disclosure if the transaction is honest. If the result of such examination may often be a considerable amount of immaterial testimony, this is a much less evil than to stifle examination by technical rules which would defeat the purpose of the act and discredit the administration of the law in the interest of the creditors." *In Re Drexel Burnham,* 123 B.R at 709.

39. The NAS Children Ad Hoc is requesting the Court to allow it to conduct examination of subject matter that is both tailored and purposeful.

c. <u>Good Cause Has Been Adequately Demonstrated.</u>

40. The foregoing facts and arguments, and those set forth in the Motion, demonstrate good cause to grant the relief sought.

41. Additionally, the NAS Children Ad Hoc contends that its requests are applicable to both the Debtors and non-parties, alike, while also acknowledging that if a non-debtor objects the party seeking the examination must demonstrate "good cause". When this occurs, courts generally apply a "totality of the circumstances" or balancing test to determine whether "good cause" exists. *See In re AOG Enm't, Inc.*, 558 B.R. 98 (Bankr. S.D.N.Y. 2016. In sum, the NAS Children Ad Hoc contends that, notwithstanding its position that it need not demonstrate good cause to conduct examinations of the person identified in the Motion, it has, nonetheless, come forward with facts and arguments demonstrating good cause for these examinations to proceed.

CONCLUSION

42. The NAS Children Ad Hoc respectfully requests that the Court enter an order, substantially in the form previously submitted authorizing the NAS Children Ad Hoc to issue discovery and undertake a Rule 2004 examination of the Records Custodian(s) of the Debtors, and other individuals.

Dated: March 19, 2021
New York, New York

Respectfully Submitted,

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EXHIBIT A

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UNITED STATES BANKRUPTCY COURT
SOUTHERN DISTRICT OF NEW YORK

In re:	:	Chapter 11
PURDUE PHARMA L.P., *et al*.,	:	Case No. 19-23649 (RDD)
Debtors.[1]	:	(Jointly Administered)

DECLARATION OF DONALD CREADORE, ESQ. IN SUPPORT OF REPLY OF THE NAS CHILDREN AD HOC IN FURTHER SUPPORT OF ITS REQUEST FOR ENTRY OF A COURT ORDER AUTHORIZING EXAMINATIONS PURSUANT TO FEDERAL RULES OF BANKRUPTCY PROCEDURE 2004 AND 9006.

Under 28 U.S.C. § 1746, I, Donald Creadore, declare under the penalty of perjury that the following is true and correct to the best of my knowledge, information, and belief:

[1] The Debtors in these cases, along with the last four digits of each Debtor's registration number in the applicable jurisdiction, are as follows: Purdue Pharma L.P. (7484), Purdue Pharma Inc. (7486), Purdue Transdermal Technologies L.P. (1868), Purdue Pharma Manufacturing L.P. (3821), Purdue Pharmaceuticals L.P. (0034), Imbrium Therapeutics L.P. (8810), Adlon Therapeutics L.P. (6745), Greenfield BioVentures L.P. (6150), Seven Seas Hill Corp. (4591), Ophir Green Corp. (4594), Purdue Pharma of Puerto Rico (3925), Avrio Health L.P. (4140), Purdue Pharmaceutical Products L.P. (3902), Purdue Neuroscience Company (4712), Nayatt Cove Lifescience Inc. (7805), Button Land L.P. (7502), Rhodes Associates L.P. (N/A), Paul Land Inc. (7425), Quidnick Land L.P. (7584), Rhodes Pharmaceuticals L.P. (6166), Rhodes Technologies (7143), UDF L.P. (0495), SVC Pharma L.P. (5717) and SVC Pharma Inc. (4014).

1. This declaration ("Declaration") is submitted in support of ***Reply Of The NAS Children Ad Hoc In Further Support Of Its Request For Entry Of A Court Order Authorizing Examinations Pursuant To Federal Rules Of Bankruptcy Procedure 2004 And 9006*.**

2. I am an attorney in good standing admitted to practice in the State of New York. I make this Declaration based on my own personal knowledge and belief, and upon documents and information available to me as counsel to NAS Children Ad Hoc Committee.

3. Attached hereto as **Exhibit A, B, C-1**, **C-2**, and **C-3** filed together with this Declaration, are true and accurate copies of documents adduced during discovery in this matter and during discovery in ***In re National Prescription Opioid Litigation, MDL 2084.***

4. Attached hereto as **Exhibit D**, filed together with this Declaration, is a true and accurate copy of revised requests for production related to ***Reply Of The NAS Children Ad Hoc In Further Support Of Its Request For Entry Of A Court Order Authorizing Examinations Pursuant To Federal Rules Of Bankruptcy Procedure 2004 And 9006*.**

5. Attached as **Exhibit E**, filed together with this Declaration, is a true and accurate copy of the 9th Edition of Drugs in Pregnancy and Lactation medical reference guide, a publicly available document.

6. Attached as **Exhibit F**, filed together with this Declaration, is a true and accurate copy of email exchanges generated by counsel for the NAS Children Ad Hoc Committee and the Debtors.

7. Attached as **Exhibit G and H,** filed together with this Declaration, are true and accurate copy of E-mail communications adduced during discovery in this matter and during discovery in ***In re National Prescription Opioid Litigation, MDL 2084.***

Dated: NEW YORK, NY

Respectfully submitted this 19th day of March, 2021:

/s/ Donald Creadore o/b/o NASS Children Ad Hoc Committee

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Exhibit A

Exhibit B

[redacted]

[redacted]

II. APPLICATION SUMMARY 11

[redacted]

Exhibit C-1

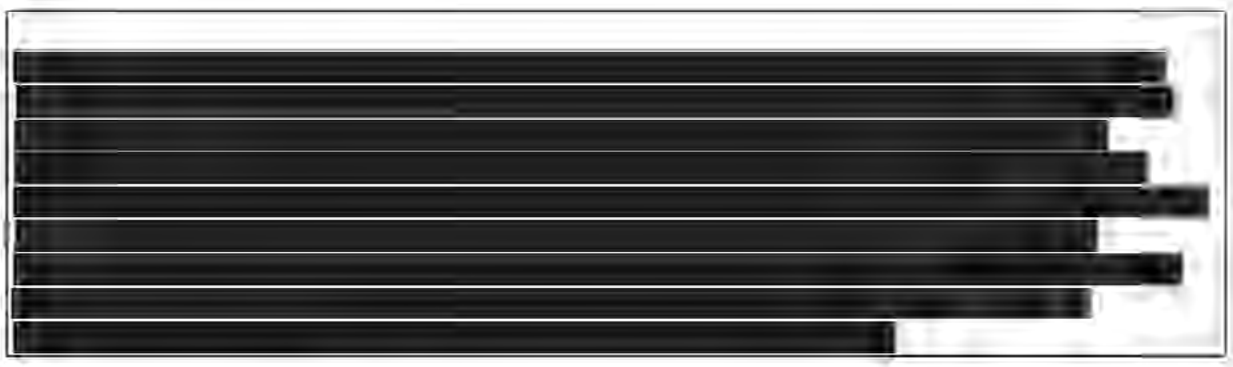

Exhibit C-2

Exhibit C-3

[redacted]

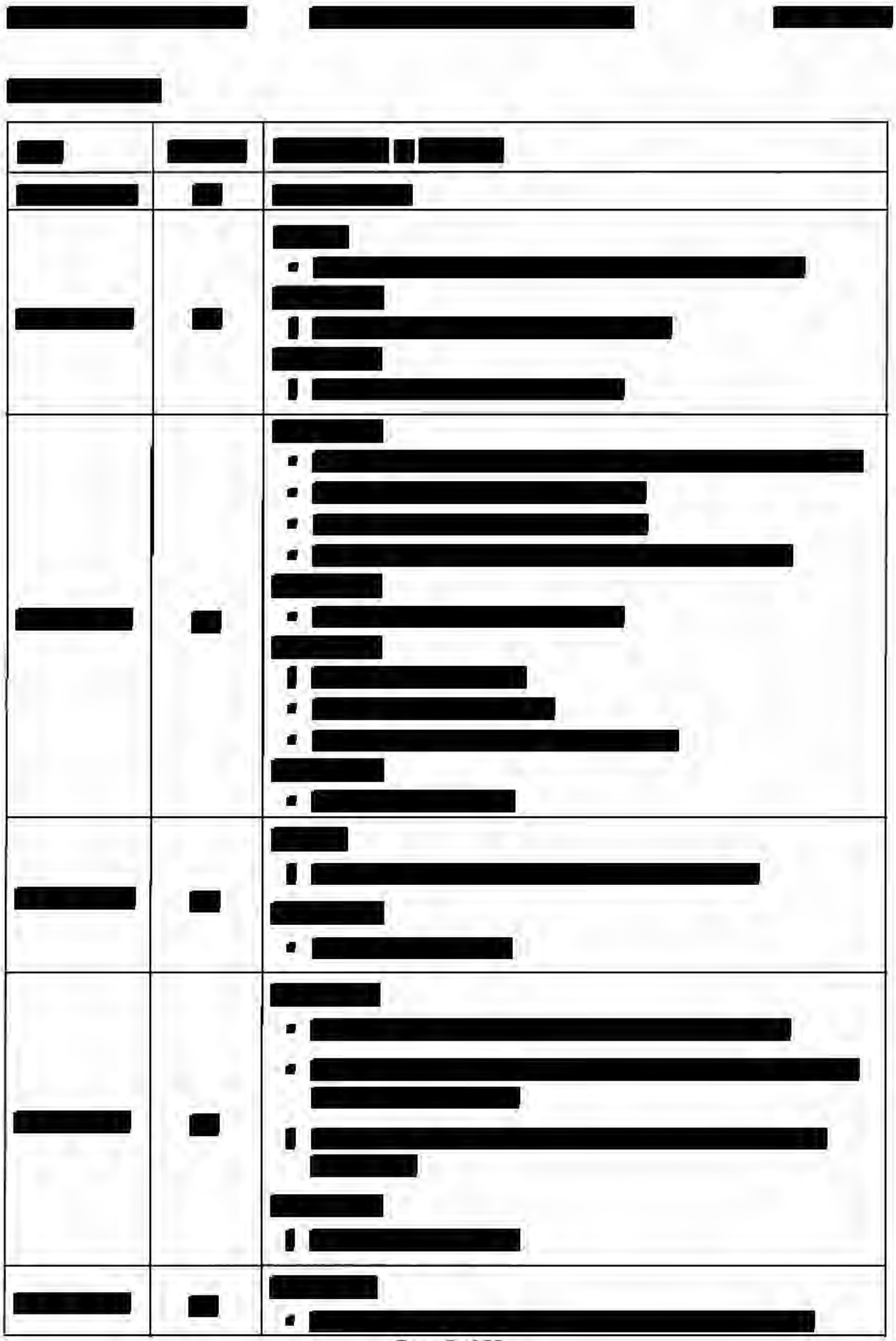

Exhibit D

[redacted]

[redacted]

1. [redacted]

2. [redacted]

3. [redacted]

Exhibit E

BUPRENORPHINE

Risk Factor: C_M

Narcotic Agonist-Antagonist Analgesic

FETAL RISK RECOMMENDATION: Limited Human Data - Animal Data Suggest Low Risk

BREAST FEEDING RECOMMENDATION: Limited Human Data - Potential Toxicity

FETAL RISK SUMMARY

Buprenorphine, an analgesic that possesses both narcotic agonist and antagonist activity, is approximately 33 times more potent than morphine (0.3 mg buprenorphine is equivalent to 10 mg morphine in analgesic and respiratory depressant effects). Although a sublingual formulation is available in other countries, only parenteral buprenorphine has been approved for general use in the United States. The human adult dose is 0.3–0.6 mg IM or IV repeated up to every 6 hours (0.017–0.034 mg/kg/day for a 70-kg person).

Buprenorphine is currently under investigation as an alternative to methadone maintenance treatment of narcotic dependence (1–3). The drug has also been studied as an alternative to cocaine, but it is apparently not effective for this use (2). Although these trials have not yet included pregnant women, the advantages of buprenorphine over methadone during gestation may include less respiratory depression at high doses, less toxicity from overdose, less severe withdrawal after abrupt discontinuance of the drug, and potentially less abuse liability (1,2). Of interest, however, abuse of buprenorphine, often concurrently with opiates, has been reported outside of the United States (4,5). One of these latter citations reported frequent abuse of buprenorphine by pregnant women but provided no outcome data (4).

Reproduction studies in rats and rabbits have been conducted (6–12). No fetal adverse effects were observed in rats and rabbits when their mothers were administered doses <5 mg/kg IM during organogenesis (6). Shepard cited a study in which fetal growth retardation, but not congenital defects, was observed in rats exposed to maternal doses of >0.05–5 mg/kg/day (about 3–300 times the recommended human dose [RHD]) given after implantation through delivery (7). Rat fetuses exposed to 5 mg/kg/day in the last week of pregnancy had a reduced survival rate after delivery (7). As reported by the manufacturer, no major congenital malformations were observed in rats given doses of 10–1000 times (SC or IM) or 160 times (IV) the RHD, but significant increases in postimplantation losses and early fetal deaths were noted with IM doses of 10 and 100 times the RHD (8). A slight increase in postimplantation losses was also observed with IV doses of 40 and 160 times the RHD. In rabbits, IM doses produced a dose-related increase in extra rib formation that was statistically significant at 1000 times the RHD (8). Rat pups exposed in utero throughout gestation to maternal doses of buprenorphine, 1 and 2 mg/kg/day SC, had reduced survival. Minimal effects were observed on the endogenous opioid system, however, as determined by a comparison of the brain enkephalin levels of buprenorphine-exposed pups with those in methadone-exposed pups (9).

In a study involving pregnant rats, buprenorphine was administered by a continuous infusion in doses of 0.3, 1.0, and 3.0 mg/kg/day from day 8 of gestation through parturition (10). At these doses, no evidence of significant maternal toxicity was observed, nor were there any significant effects on the offspring in terms of morbidity and mortality, birth weight, and postnatal growth (<60 days) (10). In a second publication by these

B

researchers, using the same drug-administration technique and animal type described above, no disruption in the rest–activity cycle was observed in the exposed offspring at 22 and 30 days of age (11).

The long-term effects on sexual differentiation in rats exposed in utero to maternal injections of buprenorphine, 0.3 or 0.6 mg/kg every 48 hours from day 6 to day 20 of gestation, were described in a study published in 1997 (12). Compared with controls and the lower-dose group, spontaneous parental behavior (at 23–28 days of age) and the expected sex difference in the consumption of a 0.25% saccharin solution (at 42–55 days of age) were impaired in the 0.6-mg/kg-exposed offspring. The authors concluded that the higher dose of buprenorphine produced long-term adverse effects on behavior (12).

As suggested by the molecular weight of the free base (about 468), buprenorphine crosses the placenta to the fetus. In a 1997 case report, a 24-year-old woman was treated with buprenorphine 4 mg/day for heroin addiction, starting in the fourth month of pregnancy (13). Frequent tests during the remainder of the pregnancy and at delivery confirmed her rapid withdrawal from heroin. Except for buprenorphine, all tests were negative for opiates, cocaine, cannabis, and amphetamines. An apparently normal female infant (birth weight not specified) was delivered at 39 weeks' gestation. Apgar scores were 10 and 10 at 1 and 10 minutes, respectively. High levels of buprenorphine and its metabolite were measured in the newborn approximately 20 hours after birth. Maternal trough serum concentrations of buprenorphine and the metabolite norbuprenorphine obtained a few days before delivery were 0.3 and 2.3 ng/mL, respectively. Parent drug and metabolite concentrations in the meconium were 107 and 295 ng/g, respectively. Levels of drug and metabolite were, respectively, 1.9 and 1.7 ng/mL in the newborn's serum and 36.8 and 61.1 ng/mL in the newborn's urine. The estimated cord:maternal serum ratio was 6.3, whereas the ratio for the metabolite was 0.7. A weak withdrawal syndrome was observed at 48 hours of age with an adapted Finnegan score (used to evaluate the intensity of withdrawal syndromes; range 0–40) of 12 (13). Symptoms, which resolved without therapy, consisted of agitation, sleep disturbance, tremor, yawning, noisy breathing, and a slight fever (13). The Finnegan score fell to 8 at 3 days of age and was normal by 6 days of age.

The effect of epidural buprenorphine combined with bupivacaine has been compared with epidural combinations of bupivacaine and morphine, fentanyl, sufentanil, and oxymorphone for analgesia during and after cesarean section (14–17). The analgesic effects of the narcotic agents were similar, but buprenorphine caused a significant increase in maternal vomiting (14–16). No adverse neonatal effects were observed in the two studies that used buprenorphine before delivery (14,17).

The use of sublingual buprenorphine for labor pain in 34 primigravida women was described in a 1992 report (18). Each patient received a single 6-mcg/kg dose during the first stage of labor. No effects were observed on the progression of labor, and none of the women had nausea or vomiting. Similarly, no changes in fetal heart rate (range 138–150 beats/minute) were observed. Buprenorphine produced no neonatal depression as evidenced by the average Apgar scores (range not specified) at 1 and 5 minutes of 9.71 and 9.94, respectively.

SUMMARY: Buprenorphine is a potent narcotic agonist and antagonist that has been used during human pregnancy for analgesia immediately prior to delivery in a small number of cases. Only one pregnancy case has been located in which the drug was given as a narcotic substitute for heroin dependency. Neonatal withdrawal was observed, but the symptoms were less than that expected with methadone. Animal studies have demonstrated dose-related maternal, embryo, and fetal toxicity and dose-related behavioral changes in offspring, but no congenital malformations. Although the lack of congenital anomalies

is reassuring, the behavioral changes in animals combined with the absence of published early human pregnancy experience prevent an assessment of the risk this drug presents to the embryo or fetus. Because there is substantially more published human pregnancy experience for other narcotic analgesics, they are preferred to buprenorphine, especially during early gestation. Buprenorphine may have a role as substitution therapy for maternal heroin addiction, but additional reports are needed to define its pregnancy safety profile before this use can be recommended.

BREAST FEEDING SUMMARY

Buprenorphine is excreted into human milk. In a 1997 case report (see above), a 24-year-old former heroin addict on buprenorphine maintenance therapy (4 mg/day) gave birth to an apparently normal female infant at 39 weeks' gestation (13). She continued taking buprenorphine while nursing her infant. At 4 weeks of age, buprenorphine and its metabolite, norbuprenorphine, were determined in her milk at each feeding over a 24-hour period. The volume of milk drunk was estimated by weighing the infant before and after the feedings. Although the specific milk concentrations were not provided, the authors estimated that the total doses of drug and metabolite ingested by the infant over the 24-hour period were 3.28 and 0.33 mcg, respectively. No withdrawal symptoms in the infant were observed when lactation was abruptly interrupted at 8 weeks of age.

A study published in 1997 described the effects of continuous extradural bupivacaine and buprenorphine on analgesia and breastfeeding in 20 healthy women who had undergone a cesarean section at term (19). The study group ($N = 10$) received a 5-mL bolus of bupivacaine 0.25% with 200 mcg of buprenorphine extradurally at cord clamping, followed by a continuous extradural infusion of bupivacaine (0.25%) and buprenorphine (12 mcg/mL) infused at 0.7 mL/hour for 3 days. The control group ($N = 10$) received the same bolus and continuous infusion, but without the buprenorphine. There were no significant differences in visual analogue pain scores between the groups at 2 hours, 1 day, and 2 days, but the controls received significantly more supplemental diclofenac (a nonsteroidal anti-inflammatory agent) during the 2-day period (mean 25 mg vs. 5 mg, $p < 0.05$). The weight of breast milk ingested at each feeding was estimated by weighing the infant before and after each feeding. Compared with the control group, the buprenorphine group ingested significantly less milk each day (starting at day 3), and the infant's daily weight as a percentage of birth weight was significantly less starting at day 7. In both effects, the significant differences continued up to 11 days, near the time of discharge from the hospital. The investigators speculated that the differences between the two groups might be due to central nervous system depression in the mother and infant. Although one author thought the stress of the prolonged hospital stay may have depressed the breast feeding (20), the investigators responded that long hospital stays are normal in Japan and, if stress is a factor, would have affected both groups similarly (19).

Because buprenorphine is excreted into milk and because depression of the nursing infant resulting in lower weight gain is a possibility, mothers receiving buprenorphine should probably not breastfeed. If breastfeeding is undertaken, the mother should be advised of the potential risk to her infant.

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O

OXYCODONE

Narcotic Agonist Analgesic

FETAL RISK RECOMMENDATION: Human Data Suggest Risk in 3rd Trimester

BREAST FEEDING RECOMMENDATION: Limited Human Data - Probably Compatible

Risk Factor: B_M*

FETAL RISK SUMMARY

Oxycodone is a narcotic analgesic available as a single agent or in combination with nonnarcotic analgesics, such as acetaminophen or aspirin. Reproduction studies in rats and rabbits at doses up to 4 and 60 times the human dose of 120 mg/day in a 60-kg adult (0.7 and 19 times the human dose based on BSA), respectively, found no evidence of fetal harm (1).

The Collaborative Perinatal Project monitored 50,282 mother–child pairs, 8 of whom had 1st trimester exposure to oxycodone (2). No evidence was found to suggest a relationship to large categories of major or minor malformations or to individual defects.

In a surveillance study of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 281 newborns had been exposed to oxycodone during the 1st trimester (F. Rosa, personal communication, FDA, 1993). A total of 13 (4.6%) major birth defects were observed (12 expected), including (observed/expected) 3/3 cardiovascular defects and 1/1 hypospadias. No anomalies were observed in four other defect categories (oral clefts, spina bifida, polydactyly, and limb reduction defects) for which specific data were available. These data do not support an association between the drug and congenital defects.

At a 1996 meeting, data was presented on 118 women using oxycodone ($N = 78$) or hydrocodone ($N = 40$) during the 1st trimester for postoperative pain, general pain, or upper respiratory infection who were matched with a similar group using codeine for

these purposes (3). Six (5.1%) of the infants exposed to oxycodone or hydrocodone had malformations, an odds ratio of 2.61 (95% confidence interval 0.6–11.5; $p = 0.13$). There was no pattern evident among the six malformations.

A 26-year-old woman with chronic pain and depression took oxycodone, 60 mg/day, quetiapine, 400 mg/day, and fluoxetine, 40 mg/day, throughout pregnancy (4). She gave birth at 37 weeks' gestation to an apparently normal 3.4-kg (50th percentile) male infant and then continued these drugs during breastfeeding. The infant's weight at 3 months of age was 5.6 kg (25th percentile), but the Denver Development Assessment was consistent with his chronological age (4).

*[*Risk Factor D if used for prolonged periods or in high doses at term.]*

BREAST FEEDING SUMMARY

Oxycodone is excreted into breast milk. Six healthy postpartum women received a combination product of oxycodone and acetaminophen, one or two capsules every 4–7 hours, while breastfeeding their newborn infants (5). Maternal plasma levels were in the expected range of 14–35 ng/mL, and milk concentrations ranged from <5–226 ng/mL. Peak milk concentrations occurred 1.5–2.0 hours after the first dose, and then at variable times after multiple doses. Although a large degree of variability was present, the mean milk:plasma ratio was 3.4:1. No mention was made of any effects observed in the nursing infants.

Although occasional maternal doses of oxycodone for analgesia probably present a minimal risk for adverse effects during nursing, infants should be monitored for gastrointestinal effects, sedation, and changes in feeding patterns.

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HYDROCODONE

Risk Factor: C*

Narcotic Agonist Analgesic, Respiratory Drug (Antitussive)

FETAL RISK RECOMMENDATION: Human Data Suggest Risk in 3rd Trimester

BREAST FEEDING RECOMMENDATION: No Human Data - Probably Compatible

FETAL RISK SUMMARY

Hydrocodone is a centrally acting narcotic agent that is related to codeine. It is combined with other drugs for use as an analgesic or as an antitussive. In a reproductive study in hamsters, a single SC injection (102 mg/kg) during the critical period of central nervous system organogenesis produced malformations (cranioschisis and various other lesions) in 3.4% of the offspring (1). Because of its narcotic properties, withdrawal could theoretically occur in infants exposed in utero to prolonged maternal ingestion of hydrocodone.

In a surveillance study of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 332 newborns had been exposed to hydrocodone during the 1st trimester (F. Rosa, personal communication, FDA, 1993). A total of 24 (7.2%) major birth defects were observed (14 expected), 5 of which were cardiovascular defects (3 expected). No anomalies were observed in five other defect categories (oral clefts, spina bifida, polydactyly, limb reduction defects, and hypospadias) for which specific data were available. The total number of malformations is suggestive of a possible association, but other factors, including the mother's disease, concurrent drug use, and chance, may be involved.

At a 1996 meeting, data on 118 women using hydrocodone ($N = 40$) or oxycodone ($N = 78$) during the 1st trimester for postoperative pain, general pain, or upper respiratory infection were matched with a similar group using codeine for these purposes (2). Six (5.1%) of the infants exposed to hydrocodone or oxycodone had malformations, an odds ratio of 2.61 (95% confidence interval [CI] 0.6–11.5) ($p = 0.13$). There was no pattern evident among the six malformations.

*[*Risk Factor D if used for prolonged periods or in high doses at term.]*

BREAST FEEDING SUMMARY

No reports describing the use of hydrocodone during human lactation have been located. The molecular weight (about 381) is low enough for excretion into breast milk. Although occasional maternal doses of hydrocodone probably represent a minimal risk during nursing, infants should be monitored for gastrointestinal effects, sedation, and changes in feeding patterns.

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Exhibit F

Gmail [redacted]

[redacted]

donald@creadorelawfirm.com <donald@creadorelawfirm.com> Tue, Mar 9, 2021 at 12:30 PM
To: Will Kovalchik <willkoval@gmail.com>
Cc: don creadore <Donald@creadorelawfirm.com>, Kevin Thompson <kwthompsonwv@thompsonbarneylaw.com>

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Exhibit G

Exhibit H

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